corresponding to the data summarized on page 9, lines 10-15, appears in the specification. The specification has been amended accordingly to remove reference to a Table 7 on this page, to renumber the remaining successive tables correctly as Table 7 (at page 41) and Table 8 (at page 61), and to correctly identify these tables within the text at page 41, lines 2-3, and page 61, lines 10-11. In addition, the specification has been amended at page 34, line 12, to correctly identify the data presented in Table 5 as representing scores for "treatment satisfaction" as opposed to "angina frequency," which is the data shown in Table 4.

This continuation-in-part (CIP) application was filed to submit the results of the proposed phase II clinical trial referred to in Example 4 of parent application U.S. Serial No. 09/385,114. The specification for this CIP application inadvertently includes the text for the original Example 4 of the parent application. Accordingly, the specification has been amended at page 51, lines 9-17, to delete the text for original Example 4, at page 51, line 20, to renumber Example 5 as Example 4, accordingly; and at page 52, line 16, to renumber Example 6 as Example 5, accordingly, and to insert the amended title for original Example 4 to reflect the phase II clinical trial described in this example.

Support for these amendments to the specification can be found throughout the specification. No new matter is added by way of these amendments. The Examiner is respectfully requested to enter these amendments into the present application.

The Rejections of the Claims Under 35 U.S.C. §103 Should Be Withdrawn

Claims 35, 36, 43, and 44 are rejected under 35 U.S.C. §103 as being unpatentable over Deisher *et al.* (U.S. Patent No. 5,989,866). Claims 37 and 45 are rejected under 35 U.S.C. §103 as being unpatentable over Deisher *et al.* in view of Fiddes *et al.* (U.S. Patent No. 5,604,293). Claims 38-41, 42, and 47-49 are rejected under 35 U.S.C. §103 as being unpatentable over Deisher *et al.* in view of Wilson *et al.* (U.S. Patent No. 5,612,211) and Unger *et al.* (U.S. Patent No. 5,244,460). These rejections are respectfully traversed.

The presently claimed invention is directed to administration of recombinant FGF-2 or administration of an angiogenically active fragment or mutein of a recombinant FGF-2 directly into one or more coronary vessels or directly into a peripheral vein of a human patient to treat a

patient suffering from congestive heart failure. Applicant respectfully submits that the cited references alone or in combination do not teach or suggest administration of recombinant FGF-2 or administration of an angiogenically active fragment or mutein of a recombinant FGF-2 directly into one or more coronary vessels or into a peripheral vein to treat human patients for congestive heart failure in accordance with the methods of the present invention.

To establish a *prima facie* case of obviousness (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP §2143. Applicant respectfully submits that when establishing a *prima facie* case of obviousness, one must consider the teachings of the cited reference(s) as a whole, including portions that would lead away from the claimed invention. MPEP §2141.02. It is Applicant's contention that a *prima facie* case of obviousness has not been established in the present application as the motivation to modify any one of these references, or to combine the teachings of these references, to arrive at Applicants' claimed invention is lacking. Even if such motivation were to exist, these references do not provide to one of skill in the art a reasonable expectation of success. Further, these references fail to teach or suggest all of the limitations set forth in the pending claims.

Deisher *et al.* serves as the primary reference cited by the Examiner. This reference teaches novel polynucleotides and polypeptide molecules of zFGF-5, which the patentees have assigned to the FGF family based on sequence homology. Thus, Deisher *et al.* provide a homology alignment with zFGF-5 and human FGF-2, indicating that they are only 31% homologous. This cited reference teaches that zFGF-5 is most closely related to FGF-8, which is structurally and functionally different from FGF-2. See this cited reference at column 8, lines 63-67, where it is stated that "[m]any FGF family members can be placed into one of two related families on the basis of their structures and functions." Deisher *et al.* further state that aFGF (FGF-1) and bFGF (FGF-2) consist of three exons separated by two introns, while FGF-8 consists of five exons. Therefore, FGF-2 and zFGF-5 are disclosed as being very different growth factors, both structurally and functionally. Deisher *et al.* describe two ways the various

FGFs exert specificity of activity: the first is their degree of affinity for each of the four FGF receptors, and the second is the spatial and temporal expression of the ligands and their receptors (column 1, lines 47-52). This cited reference also reports that expression of zFGF-5 is highest in fetal and adult heart tissue, followed by fetal lung, skeletal muscle, and smooth muscle tissues (column 7, line 63, through column 8, line 1). In contrast, Fiddes *et al.* report that FGF-2 was isolated from brain, adrenal gland, corpus luteum, retina, kidney, and placenta (see, U.S. Patent No. 5,604,293, column 5, lines 1-4).

Thus, Deisher *et al.*'s invention is directed to an entirely different molecule having structural and functional features that distinquish it from other members of the FGF family, more particularly from FGF-2, to which Applicant's invention is addressed. Based on this fact alone, one of skill in the art would not have been motivated to substitute the distantly related FGF-2 molecule into the invention of Deisher *et al.*, and then to further modify Deisher *et al.*'s invention in order to arrive at Applicant's claimed invention.

Furthermore, while Deisher *et al.* disclose a long list of uses for zFGF-5 polypeptides, including treating congestive heart failure and promoting angiogenesis, they provide no evidence to suggest a reasonable expectation of success with the zFGF-5 molecule, particularly for treatment of a human patient for congestive heart failure. Applicant also respectfully notes that Deisher *et al.* do not teach or suggest a method for treating a human patient for congestive heart failure comprising administering an angiogenically active fragment or mutein of FGF-2, as the Examiner asserts in the Office Action (at page 3, paragraph 1).

In fact, Deisher *et al.* provide no evidence that zFGF-5 or its muteins have angiogenic activity or mitogenic activity for endothelial cells. The examples set forth in this patent measure the *in vivo* mitogenic activity of adenovirus-produced zFGF-5 on cultured murine myocytes inoculated with an adenoviral-zFGF-5 construct (Example 3B), *in vivo* mitogenic activity of a zFGF-5-MBP (maltose binding protein) fusion on cultured murine myocytes (Example 3C), and *ex vivo* mitogenic activity of a zFGF-5-Hep2 fusion on left and right ventricles isolated from mice (Example 4), all by measuring ^{3}H-thymidine incorporation. Deisher *et al.* prophetically measure the effect of intraperiocardially injected zFGF-5 on cardiac regeneration in neonatal and adult rats by determining heart weight and function (Example 5). Other *in vivo* examples

demonstrate mitogenic activity of adenovirus-produced zFGF-5 on murine osteoblasts (Example 7B) and reportedly demonstrate an increase in murine heart size when an adenoviral-zFGF construct comprising zFGF-5 is administered IV to mice (Example 8). None of these examples were designed to measure angiogenic activity of the zFGF-5 molecule or its mitogenic activity on endothelial cells.

Applicant respectfully submits that such evidence would hardly be interpreted by one of skill in the art as providing the basis for a reasonable expectation of success for the use of zFGF-5, to treat human patients with congestive heart failure. Nor does this evidence suggest to one of skill in the art that FGF-2, a remotely related member of the FGF family, should be administered into one or more coronary arteries or into a peripheral vein of a patient in need of treatment for congestive heart failure. Furthermore, when describing the isolation of muteins for use in their invention, Deisher *et al.* state that the biological activity to test for is proliferation of cardiac myocytes or fibroblasts, or stimulation of bone formation (see column 14, lines 1-3), not angiogenic activity or even proliferation of endothelial cells.

The invention of Deisher *et al.* is focused on using zFGF-5 to stimulate the proliferation of myocytes, resulting in remodeling of the heart tissue and renewal of the heart's ability to function, and osteoblasts, enhancing osteoblast-mediated bone formation. Though this cited reference suggests that zFGF-5 would have angiogenic activity based on its homology to other members of the family of FGF molecules, it provides no credible evidence that zFGF-5, or any of the mutein zFGF-5 molecules described by Deisher *et al.*, has angiogenic activity or would be useful for treating congestive heart failure in a human.

With regard to the statement by Deisher *et al.* that FGF-2 has been shown to play a role in avian cardiac development and that it induces coronary collateral development in dogs, it was well known to those skilled in the art that animal models of myocardial ischemia were unreliable and often produced opposing results (see page 3, lines 8-10, of the instant specification). The canine model in particular has been criticized for its "abundance of naturally occurring collateral circulation" (see page 3, lines 10-12, of the instant specification). Therefore, it would not have been obvious to use FGF-2 to treat congestive heart failure based on these limited findings for avian and canine cardiac development.

Applicant further notes that the present invention is based upon phase I and phase II clinical trials with human patients having CAD, including a subset of patients with congestive heart failure. Administration of FGF-2 in the manner set forth in the present invention unexpectedly provided these human patients with a rapid and therapeutic coronary angiogenesis that resulted in an unexpectedly large increase in the treated patients' exercise tolerance time (ETT) that persisted for an unexpectedly long duration (see the specification at page 4, lines 3-11). Improvements in ETT were seen at all doses tested for the subset of patients with congestive heart failure (see the specification at page 66, lines 20-22). Such a therapeutic benefit could not have been predicted or expected by those of skill in the art based on the teachings of Deisher *et al.*, which clearly would be view by those of skill in the art as a genomics application directed to a distant member of the FGF family.

For all of these reasons, Applicant respectfully submits that the Deisher *et al.* reference cannot serve as the basis for a *prima facie* case of obviousness. This reference provides no motivation to one of skill in the art to modify the teachings of Deisher *et al.* to arrive at Applicant's claimed invention, nor does it provide a reasonable expectation of success in doing so. Finally, it does not teach or suggest all of the limitations recited in the rejected claims. In view of these remarks, Applicant respectfully submits that this rejection should be withdrawn.

The Examiner further relies on the combination of Deisher *et al.* and Fiddes *et al.* (U.S. Patent No. 5,604,293) to reject claims 37 and 45. However, Applicant respectfully notes that the combination of these references also does not establish a *prima facie* case of obviousness for the following reasons.

As noted above, the focus of Deisher *et al.* is on use of a distantly related FGF family member to effect proliferation of cardiac myocytes and remodeling of cardiac tissue or proliferation of osteoblasts to effect bone formation. Deisher *et al.* provides no evidence of angiogenic activity of the novel zFGF-5 molecule, nor does this reference teach the use of an angiogenically active fragment or mutein of zFGF-5. Rather, Deisher *et al.* demonstrate mitogenic activity of zFGF-5 on murine cardiac myocytes and murine osteoblasts, and teach the means for determining the mitogenic activity of muteins of this sequence on these cell types.

Though Deisher *et al.* mention congestive heart failure as one of several clinical indications that could be treated using the zFGF-5 molecules, their experimental evidence provides no reasonable expectation of success for treating a human patient with congestive heart failure.

Fiddes *et al.* disclose the synthesis and manipulation of acidic (FGF-1) and basic (FGF-2) fibroblast growth factors and suggest that these sequences are useful in effecting a number of responses, including accelerated healing of wounds, bone fractures, burn tissue, degenerated neurological tissue, damaged myocardial tissue, or other trauma. As with Deisher *et al.*, this is a genomics application directed to isolation of specific members of the FGF family. The only evidence of therapeutic utility for the claimed sequences resides in Example 12, where the potential for FGF-2 activity to promote wound healing is demonstrated using subcutaneous implantation of bovine FGF-2-soaked polyvinyl alcohol sponges into rats. Fiddes *et al.* suggest intravenous administration of FGF-1 and FGF-2 for treatment of conditions that respond to tissue plasminogen activator or collagenase (column 8, lines 30-32). However, Fiddes *et al.* are silent with respect to administration of FGF-2 into coronary vessels or into a peripheral vein of a human patient in need of treatment for congestive heart failure. This specific claim limitation is also not taught or suggested by Deisher *et al.*, who merely state that their molecules can be formulated as pharmaceutical compositions for parenteral administration, such as intravenously or subcutaneously (see Deisher *et al.* at column 26, lines 36-40), without guidance as to location of intravenous injection or infusion. Applicant respectfully submits that one of skill in the art would readily recognize the Fiddes *et al.* patent as teaching novel genomic sequences, with a mere suggestion of their use in treating a number of clinical indications, and no reasonable expectation of success for their use in treating congestive heart failure.

The Office Action states that it would have been obvious to one of ordinary skill in the art at the time the present invention was made to modify the invention of Deisher *et al.* to treat congestive heart failure using the FGF-2 protein disclosed by Fiddes *et al.* because the requisite motivation and expectation of success are provided by the statement by Deisher *et al.* that FGF-2 has been shown to play a role in avian cardiac development and coronary collateral development in dogs, and Fiddes *et al.*'s disclosure of administration of FGF-2 (Office Action mailed November 15, 2002, at page 4, last paragraph, continuing through line 2 of page 5). Applicant

respectfully disagrees. Rather, one of skill in the art would recognize that such limited observations in avian and canine models are not readily applicable to humans for reasons noted above and further elaborated on in the present specification (at page 3). Further, Deisher *et al.* cannot reasonably be interpreted as providing evidence that zFGF-5 or FGF-2 can effectively treat a human patient with congestive heart failure, or providing the requisite guidance to practice the presently claimed invention. Such evidence and guidance are also not provided by the Fiddes *et al.* reference.

In view of these remarks, Applicant respectfully submits that the Deisher *et al.* and Fiddes *et al.* references, alone or in combination, do not teach or suggest all of the limitations of Applicant's claimed invention. Therefore, a *prima facie* case of obviousness has not been established, and this rejection of the claims should be withdrawn.

As to the rejection of claims 38-41, 42, and 47-49 as being unpatentable over Deisher *et al.* in view of Wilson *et al.* (U.S. Patent No. 5,612,211) and Unger *et al.* (U.S. Patent No. 5,244,460), Applicant again respectfully notes that a *prima facie* case of obviousness has not been established. The teachings of Deisher *et al.* are discussed above. As the Examiner notes, Deisher *et al.* do not teach the claim limitation of administering heparin, particularly in combination with administration of FGF-2 into one or more coronary vessels or into a peripheral vein of a human patient to treat congestive heart failure. Applicant submits that the teachings of Wilson *et al.* and Unger *et al.* combined with the teachings of Deisher *et al.* do not teach or suggest all of the limitations of Applicant's claimed invention.

Wilson *et al.* teach the use of FGFs for the stimulation of growth, differentiation, or culture of stem cells, for subsequent use in diagnostic, therapeutic, and research applications. This cited reference also teaches the use of heparin to potentiate the stimulatory effect of "concentrations of an FGF *administered to a hematopoietic cell donor, recipient or subject according to a method of the present invention*" (at column 12, lines 52-55; emphasis added). The invention of Wilson *et al.* is directed to FGF stimulation of stem cells, either *in vivo*, or *in vitro* followed by transplantation or engraftment, for purposes of treating a long list of diseases or pathologies, though no mention is made of patients with congestive heart failure. Thus,

Applicant's contend that the motivation to combine the teachings of Wilson *et al.* with the teachings of Deisher *et al.* is lacking. Even if one of skill in the art were motivated to modify the invention of Deisher *et al.* to include administration of heparin based on the disclosure of Wilson *et al.*, such a modification would not produce Applicant's claimed invention.

The Examiner has stated that Wilson *et al.* state that FGF was used in the treatment of ischemic heart disease (U.S. Patent Nos. 4,296,100 and 4,378,347 to Franco) and refer to Arakawa *et al.* (EP 320148) as suggesting that FGF might induce neovascularization. Applicant respectfully notes that these statements in Wilson *et al.* are irrelevant to this obviousness rejection. A close review of the Franco patents shows that Franco demonstrates myocardial injection of basic FGF (bFGF) in preclinical canine and feline models of acute myocardial infarction to obtain a beneficial reduction in infarct size. The Franco patents suggest intravenous injection as a preferred mode of administration, but fail to demonstrate safety and/or efficacy in either animal model disclosed. Applicant respectfully notes that models of acute myocardial infarction are not predictive for a method of treatment for congestive heart failure, which represents a chronic ischemic condition as opposed to an acute ischemic event. Thus the beneficial results demonstrated with myocardial injection in the Franco patents and cited to in the Wilson *et al.* reference cannot be extrapolated to treatment of congestive heart failure in accordance with the methods of the present invention. In addition, a review of the Arakawa *et al.* reference also shows that the idea that FGF-2 might induce neovascularization was derived from an *in vitro* assay. Thus, the findings of Franco and Arakawa *et al.* cannot be construed as providing any reasonable expectation of success in using FGF for treating a human patient for congestive heart failure.

Unger *et al.* teach a method for treating atherosclerosis by injecting FGF-2 via a catheter into a coronary artery. The invention disclosed in this cited reference requires repeated injections until improved cardiac blood flow has been obtained. In contrast, the current invention provides a method for treating a human patient for congestive heart failure, comprising administering a therapeutically effective amount of an FGF-2 or angiogenically active fragment or mutein thereof into one or more coronary vessels or into a peripheral vein in a human patient. Administering a single unit dose of FGF-2 in accordance with the methods of the present

invention provides for coronary angiogenesis that translates into a prolonged therapeutic benefit for a subject with congestive heart failure. Such a protocol is not contemplated or even suggested by Unger *et al.* In fact, this cited reference teaches away from administration of a single unit dose of FGF-2 for congestive heart failure. See the specification at column 2, line 32, continuing through column 3, line 10, where Unger *et al.* summarize the drawbacks of the teachings of Franco, U.S. Patent No. 4,296,100, and the need for repeated injections of FGF-2 to achieve growth of blood vessels in the heart of a patient. Furthermore, Unger *et al.* do not teach administration into a peripheral vein, but limit the administration of FGF-2 to inserting a catheter into a coronary artery and providing an infusion port through which the FGF-2 composition is *repeatedly* injected. Thus Unger *et al.* fail to teach those claim limitations not taught or suggested by Deisher *et al.* and Wilson *et al.*

Thus, Applicant respectfully submits that the combined teachings of Deisher *et al.*, Wilson *et al.*, and Unger *et al.* do not render the presently claimed invention obvious, and this rejection of the claims should also be withdrawn.

In summary, one of skill in the art would not have been motivated to modify any of these cited references, or to combine the teachings of these cited references, to arrive at Applicant's invention, nor would a reasonable expectation of success have been supported by the teachings of any of these cited references. Further, these cited references alone or in combination do not teach or suggest all of the limitations recited in the pending claims. For all of these reasons, Applicant respectfully submits that a *prima facie* case of obviousness has not been established, and all of these rejections under 35 U.S.C. §103 should be withdrawn.

The Objections to the Claims Should Be Withdrawn

Claims 50-52 are objected to because these claims depend from rejected claims. Applicant respectfully submits that the rejection of the base claim 45 is overcome. Accordingly, this objection to the claims should be withdrawn.

CONCLUSION

In view of the above amendments and remarks, Applicant submits that the rejections of the claims under 35 U.S.C. §103 are overcome, thereby obviating the objection to claims 50-52. Applicant respectfully submits that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Lynda-Jo Pixley

Lynda-Jo Pixley

Version with Markings to Show Changes Made:

Please amend the paragraph, beginning on page 8, line 27, and continuing through page 9, line 15, to read as follows:

As part of this study, MRI was also performed on 33 human patients diagnosed with CAD to assess the effect of administering a single unit dose of rFGF-2 on their cardiac ejection fraction, regional myocardial function and perfusion (delayed arrival zone). Specifically, the patients were administered a single unit dose of 0.33 mg/kg to 48 mg/kg IC or 18 mg/kg to 36 mg/kg IV of rFGF-2 of SEQ ID NO: 2. When the 33 human CAD patients were assessed by resting cardiac magnetic resonance imaging (MRI) at baseline (i.e., prior to treatment), and 1, 2 and 6 months after treatment with a single unit dose of rFGF-2 of the invention by IC or IV routes, the patients exhibited a highly statistically significant response to the method of treatment as objectively measured by increased target wall thickening, target wall motion, and target area collateral extent, and by decreased target area delayed arrival extent. [(Table 7)]By way of summary, at 1, 2 and 6 months, the target wall thickening increased relative to baseline at 4.4%, 6.3% and 7.7%, respectively; the target wall motion increased relative to baseline at 2.7%, 4.4% and 6.4%, respectively; the target area collateral extent increased relative to baseline at 8.3%, 10.9% and 11.2%, respectively; and the target area delayed arrival extent decreased relative to baseline at -10.0%, -8.3% and -10.0%, respectively.

Please amend the paragraph, beginning on page 34, line 11, to read as follows:

The fourth SAQ scale to be evaluated was "treatment satisfaction." The data summarizing [the angina frequency] treatment satisfaction is presented in Table 5 herein.

Please amend the paragraph, beginning on page 41, line 1, to read as follows:

The mean pharmacokinetic parameters for rFGF-2 in humans as a function of dosage and mode of administration are summarized in Table [8]7 herein. Referring to Table [8]7, the T½ for FGF-2 in humans was determined to range from 2.2 ± 3.7 hours at low dose (0.33-2.0 μg/kg) IC to 7.0 ± 3.5 hours at a dose of 18-36 μg/kg IV; given the limitations of the assay, the terminal half-life is estimated at 5-7 hours for all groups. The clearances of FGF-2 ranged from 13.2 to

18.2 L/hour/70 kg man. Finally, the steady state volume (V_{ss}) was determined to range from 11.3 ± 10.4 L/70 kg man to 16.8 ± 10.7 L/70 kg man.

Please amend the Table on page 41 to read as follows:

Table [8]7. Mean rFGF-2 PK Parameters in Humans

FGF-2 Dose µg/kg	*N*	*Route*	*CL (L/hr/70kg)*	*$t_{½}$ (h)*	*V_{ss} (L/70kg)*
0.3 - 2	16	IC	18.2±13.4	2.2± 3.7	11.3±10.4
6 - 12	8	IC	13.2± 7.3	3.1± 2.5	12.1± 4.9
24 - 48	28	IC	14.7± 8.3	6.3± 1.8	16.8 ±10.7
18 - 36	14	IV	13.9± 7.9	7.0± 3.5	16.4± 8.6

Please amend the specification to delete Example 4, on page 51.

Please amend the title for Example 5, on page 51, to read as follows:

EXAMPLE [5]4

"Unit Dose and Pharmaceutical Composition of rFGF-2 for the Phase II Human Clinical Trial"

Please amend the title for Example 6, on page 52, to read as follows:

[EXAMPLE 6] EXAMPLE 5

"Unit Dose and Pharmaceutical Composition of rFGF-2 for the Phase II Human Clinical Trial"

Please amend the paragraph beginning on page 61, line 10, to read as follows:

Table [7]8 summarizes demographic features of the subjects enrolled in the trial. These features were similar among the four treatment groups (Table [7]8).

Please amend the title for Table 7 on page 61 to read as follows:

Table [7]8 Summary of Demography